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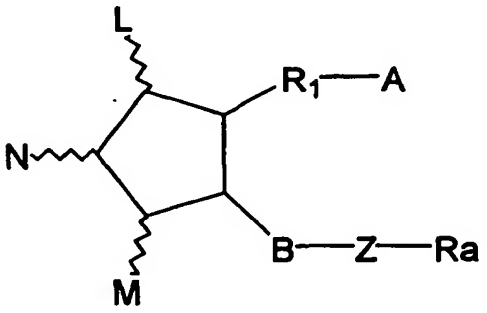
(54) Title: PROSTAGLANDIN COMPOUNDS FOR THE TREATMENT OF OBESITY



(I)

(57) Abstract: Provided is a composition for treating obesity which comprises an effective amount of a prostaglandin compound, especially, a compound of formula (I).

DESCRIPTION

PROSTAGLANDIN COMPOUNDS FOR THE TREATMENT OF OBESITY

TECHNICAL FIELD

The present invention relates to a method and composition for treating obesity.

BACKGROUND ART

Obesity, according to its cause, is classified into two groups, i.e. primary obesity (simple obesity) and secondary obesity (symptomatic obesity). The cause of primary obesity includes excessive energy intake, insufficient energy consumption and decreased thermogenesis. Today, primary obesity accounts for a large majority of diagnosed cases of obesity. Development and persistent of primary obesity may cause various health problems.

The secondary obesity is caused by certain underlying disorders and is also diagnosed as obesity. Examples of secondary obesity include endocrine obesity, hypothalamic obesity, hereditary obesity and drug-induced obesity.

Obesity is a risk factor for health. It may induce strain on the circulatory system, metabolic disorders such as diabetes, liver- or biliary- system disorders, respiratory depression as well as excessive weight on the bones and the joints.

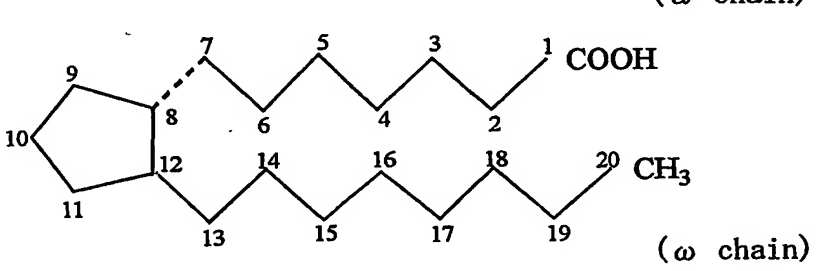
Therapeutic approaches used for treating obesity include alimentotherapy, ergotherapy, behavioral therapy,

psychotherapy and drug therapy. The alimentotherapy reduces the body weight by reducing total calorie intake with controlled diet. The method, however, often results in a lowered resting metabolic rate, which makes it harder to keep the weight off once the patient attained. Ergotherapy not only increases energy consumption, but also increases the resting metabolic rate and normalize the insulin resistance, and can effectively decrease the body fat. The big problem of the ergotherapy is the difficulty in carrying out the therapy continuously over a long period of time. The behavioral therapy and psychotherapy are carried out to support the alimentotherapy and/or ergotherapy, but they hardly bring sufficient effects.

Examples of the obesity drugs used for the drug therapy include appetite suppressant such as mazindol, fenfluramine, fluoxetine and cholecystokinin, agents to reduce digestive absorption such as acarbose, voglibose and lipostatin, agents to inhibit fat accumulation such as nafenopin, hydroxy oxalic acid and imidazole acetophen, and metabolic accelerators such as β3 receptor stimulant. However, such conventional obesity drugs may cause adverse side effects such as drug dependence, and patients having received such drugs may become resistant to the drugs in a short period. Accordingly, the conventionally used obesity drugs are not suitable for long term continuous treatment.

It has been desired in the art to develop an effective anti-obesity drug without or with decreased side effects, that can be continuously used for a long period without imposing burden on patients.

Prostaglandins (hereinafter, referred to as PG(s)) are members of class of organic carboxylic acids, which are contained in tissues or organs of human or other mammals, and exhibit a wide range of physiological activity. PGs found in nature (primary PGs) generally have a prostanoic acid skeleton as shown in the formula (A):



(A)

On the other hand, some of synthetic analogues of primary PGs have modified skeletons. The primary PGs are classified to PGAs, PGBs, PGCs, PGDs, PGEs, PGFs, PGGs, PGHs, PGIs and PGJs according to the structure of the five-membered ring moiety, and further classified into the following three types by the number and position of the unsaturated bond at the carbon chain moiety:

Subscript 1: 13,14-unsaturated-15-OH

Subscript 2: 5,6- and 13,14-diunsaturated-15-OH

Subscript 3: 5,6-, 13,14-, and 17,18-triunsaturated-15-OH.

Further, the PGFs are classified, according to the configuration of the hydroxyl group at the 9-position, into α type (the hydroxyl group is of an α-configuration) and β type (the hydroxyl group is of a β-configuration).

PGE_1 and PGE_2 and PGE_3 are known to have vasodilation, hypotension, gastric secretion decreasing, intestinal tract movement enhancement, uterine contraction, diuretic, bronchodilation and anti ulcer activities. $PGF_{1\alpha}$, $PGF_{2\alpha}$ and $PGF_{3\alpha}$ have been known to have hypertension, vasoconstriction, intestinal tract movement enhancement, uterine contraction, lutein body atrophy and bronchoconstriction activities.

However, it is not known how prostaglandin compounds act on obesity.

SUMMARY OF THE INVENTION

The present invention relates to a method for treating obesity in a mammalian subject, which comprises administration of an effective amount of a prostaglandin compound to the subject in need of such treatment.

The present invention further relates to a pharmaceutical composition for treating obesity in a mammalian subject, which comprises an effective amount of a prostaglandin compound.

Further more, the present invention relates to use of a prostaglandin compound for manufacturing a pharmaceutical composition for treating obesity in a mammalian subject.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 represents result of the example.

DETAILED DESCRIPTION OF THE INVENTION

The nomenclature of the PG compounds used herein is based on the numbering system of the prostanoic acid represented in the above formula (A).

The formula (A) shows a basic skeleton of the C-20 carbon atoms, but the present invention is not limited to those having the same number of carbon atoms. In the formula (A), the numbering of the carbon atoms which constitute the basic skeleton of the PG compounds starts at the carboxylic acid (numbered 1), and carbon atoms in the α-chain are numbered 2 to 7 towards the five-membered ring, those in the ring are 8 to 12, and those in the ω-chain are 13 to 20. When the number of carbon atoms is decreased in the α-chain, the number is deleted in the order starting from position 2; and when the number of carbon atoms is increased in the α-chain, compounds are named as substitution compounds having respective substituents at position 2 in place of the carboxy group (C-1). Similarly, when the number of carbon atoms is decreased in the ω-chain, the number is deleted in the order starting from position 20; and when the number of carbon atoms is increased in the ω-chain, the carbon atoms beyond position 20 are named as substituents. Stereochemistry of the compounds is the same

as that of the above formula (A) unless otherwise specified.

In general, each of the terms PGD, PGE and PGF represents a PG compound having hydroxy groups at positions 9 and/or 11, but in the present specification, these terms also include those having substituents other than the hydroxy group at positions 9 and/or 11. Such compounds are referred to as 9-dehydroxy- 9-substituted-PG compounds or 11-dehydroxy-11-substituted-PG compounds. A PG compound having hydrogen in place of the hydroxy group is simply named as 9- or 11-dehydroxy-PG compound.

As stated above, the nomenclature of the PG compounds is based on the prostanoic acid skeleton. However, in case the compound has a similar partial structure as a prostaglandin, the abbreviation of "PG" may be used. Thus, a PG compound of which α-chain is extended by two carbon atoms, that is, having 9 carbon atoms in the α-chain is named as 2-decarboxy-2-(2-carboxyethyl)-PG compound. Similarly, a PG compound having 11 carbon atoms in the α-chain is named as 2-decarboxy-2-(4-carboxybutyl)-PG compound. Further, a PG compound of which ω-chain is extended by two carbon atoms, that is, having 10 carbon atoms in the ω-chain is named as 20-ethyl-PG compound. These compounds, however, may also be named according to the IUPAC nomenclatures.

Examples of the analogs (including substituted

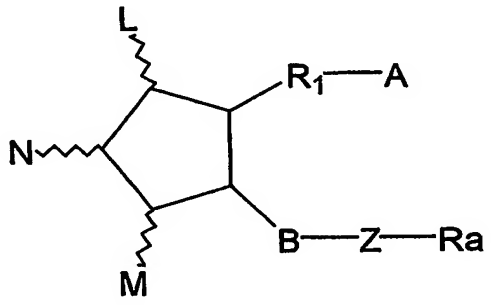
derivatives) or derivatives include a PG compound of which carboxy group at the end of α-chain is esterified; a compound of which α-chain is extended; physiologically acceptable salt thereof; a compound having a double bond at 2-3 position or a triple bond at position 5-6, a compound having substituent(s) at position 3, 5, 6, 16, 17, 18, 19 and/or 20; and a compound having lower alkyl or a hydroxy (lower) alkyl group at position 9 and/or 11 in place of the hydroxy group.

According to the present invention, preferred substituents at position 3, 17, 18 and/or 19 include alkyl having 1-4 carbon atoms, especially methyl and ethyl. Preferred substituents at position 16 include lower alkyl such as methyl and ethyl, hydroxy, halogen atoms such as chlorine and fluorine, and aryloxy such as trifluoromethylphenoxy. Preferred substituents at position 17 include lower alkyl such as methyl and ethyl, hydroxy, halogen atoms such as chlorine and fluorine, aryloxy such as trifluoromethylphenoxy. Preferred substituents at position 20 include saturated or unsaturated lower alkyl such as C1-4 alkyl, lower alkoxy such as C1-4 alkoxy, and lower alkoxy alkyl such as C1-4 alkoxy-C1-4 alkyl. Preferred substuents at position 5 include halogen atoms such as chlorine and fluorine. Preferred substituents at position 6 include an oxo group forming a carbonyl group.

Stereochemistry of PGs having hydroxy, lower alkyl or hydroxy(lower)alkyl substituent at position 9 and/or 11 may be α, β or a mixture thereof.

Further, the above analogs or derivatives may be compounds having an alkoxy, cycloalkyl, cycloalkyloxy, phenoxy or phenyl group at the end of the ω-chain where the chain is shorter than the primary PGs.

A preferred compounds used in the present invention is represented by the formula (I):



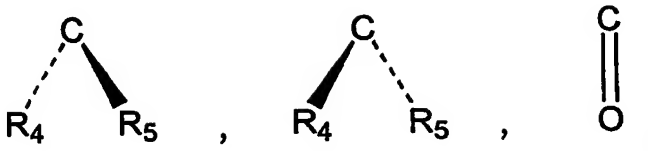
(I)

wherein L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is $-CH_3$, or $-CH_2OH$, $-COCH_2OH$, $-COOH$ or a functional derivative thereof;

B is single bond, $-CH_2-CH_2-$, $-CH=CH-$, $-C\equiv C-$, $-CH_2-CH_2-CH_2-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-C\equiv C-CH_2-$ or $-CH_2-C\equiv C-$;

Z is

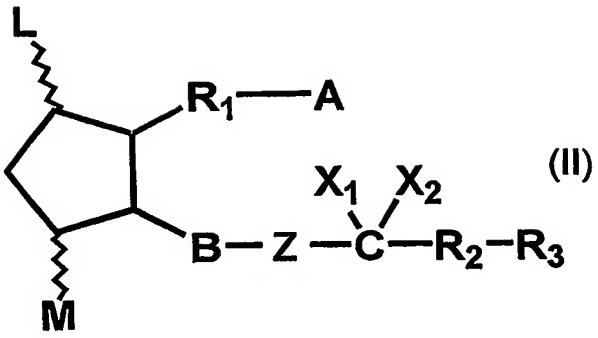
 or single bond

wherein R_4 and R_5 are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R_4 and R_5 are not hydroxy and lower alkoxy at the same time;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

Ra is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or hetrocyclic-oxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclic-oxy group.

A preferred compounds used in the present invention is represented by the formula (II):

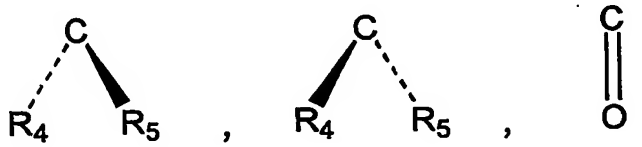


wherein L and M are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have one or more double bonds;

A is $-CH_3$, or $-CH_2OH$, $-COCH_2OH$, $-COOH$ or a functional derivative thereof;

B is single bond, $-CH_2-CH_2-$, $-CH=CH-$, $-C\equiv C-$, $-CH_2-CH_2-CH_2-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-C\equiv C-CH_2-$ or $-CH_2-C\equiv C-$;

Z is



or single bond

wherein R_4 and R_5 are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R_4 and R_5 are not hydroxy and lower alkoxy at the same time;

X_1 and X_2 are hydrogen, lower alkyl, or halogen;

R_1 is a saturated or unsaturated bivalent lower or

medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur;

R_2 is a single bond or lower alkylene; and

R_3 is lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclic-oxy group.

In the above formula, the term "unsaturated" in the definitions for R_1 and Ra is intended to include at least one or more double bonds and/or triple bonds that are isolatedly, separately or serially present between carbon atoms of the main and/or side chains. According to the usual nomenclature, an unsaturated bond between two serial positions is represented by denoting the lower number of the two positions, and an unsaturated bond between two distal positions is represented by denoting both of the positions.

The term "lower or medium aliphatic hydrocarbon" refers to a straight or branched chain hydrocarbon group having 1 to 14 carbon atoms (for a side chain, 1 to 3 carbon atoms are preferable) and preferably 1 to 10, especially 1 to 8 carbon atoms.

The term "halogen atom" covers fluorine, chlorine,

bromine and iodine.

The term "lower" throughout the specification is intended to include a group having 1 to 6 carbon atoms unless otherwise specified.

The term "lower alkyl" refers to a straight or branched chain saturated hydrocarbon group containing 1 to 6 carbon atoms and includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and hexyl.

The term "lower alkylene" refers to a straight or branched chain bivalent saturated hydrocarbon group containing 1 to 6 carbon atoms and includes, for example, methylene, ethylene, propylene, isopropylene, butylene, isobutylene, t-butylene, pentylene and hexylene.

The term "lower alkoxy" refers to a group of lower alkyl-O-, wherein lower alkyl is as defined above.

The term "hydroxy(lower)alkyl" refers to a lower alkyl as defined above which is substituted with at least one hydroxy group such as hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 1-methyl-1-hydroxyethyl. The term "lower alkanoyloxy" refers to a group represented by the formula RCO-O-, wherein RCO- is an acyl group formed by oxidation of a lower alkyl group as defined above, such as acetyl.

The term "cyclo(lower)alkyl" refers to a cyclic group formed by cyclization of a lower alkyl group as defined

above but contains three or more carbon atoms, and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "cyclo(lower)alkyloxy" refers to the group of cyclo(lower)alkyl-O-, wherein cyclo(lower)alkyl is as defined above.

The term "aryl" may include unsubstituted or substituted aromatic hydrocarbon rings (preferably monocyclic groups), for example, phenyl, tolyl, xylyl. Examples of the substituents are halogen atom and halo(lower)alkyl, wherein halogen atom and lower alkyl are as defined above.

The term "aryloxy" refers to a group represented by the formula ArO-, wherein Ar is aryl as defined above.

The term "heterocyclic group" may include mono- to tri-cyclic, preferably monocyclic heterocyclic group which is 5 to 14, preferably 5 to 10 membered ring having optionally substituted carbon atom and 1 to 4, preferably 1 to 3 of 1 or 2 type of hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom. Examples of the heterocyclic group include furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, 2-pyrrolinyl, pyrrolidinyl, 2-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl,

piperidino, piperazinyl, morpholino, indolyl, benzothienyl, quinolyl, isoquinolyl, purinyl, quinazolinyl, carbazolyl, acridinyl, phenanthridinyl, benzimidazolyl, benzimidazolinyl, benzothiazolyl, phenothiazinyl. Examples of the substituent in this case include halogen, and halogen substituted lower alkyl group, wherein halogen atom and lower alkyl group are as described above.

The term "heterocyclic-oxy group" means a group represented by the formula HcO-, wherein Hc is a heterocyclic group as described above.

The term "functional derivative" of A includes salts (preferably pharmaceutically acceptable salts), ethers, esters and amides.

Suitable "pharmaceutically acceptable salts" include conventionally used non-toxic salts, for example a salt with an inorganic base such as an alkali metal salt (such as sodium salt and potassium salt), an alkaline earth metal salt (such as calcium salt and magnesium salt), an ammonium salt; or a salt with an organic base, for example, an amine salt (such as methylamine salt, dimethylamine salt, cyclohexylamine salt, benzylamine salt, piperidine salt, ethylenediamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, tris(hydroxymethylamino)ethane salt, monomethyl- monoethanolamine salt, procaine salt and caffeine salt), a basic amino acid salt (such as arginine

salt and lysine salt), tetraalkyl ammonium salt and the like. These salts may be prepared by a conventional process, for example from the corresponding acid and base or by salt interchange.

Examples of the ethers include alkyl ethers, for example, lower alkyl ethers such as methyl ether, ethyl ether, propyl ether, isopropyl ether, butyl ether, isobutyl ether, t-butyl ether, pentyl ether and 1-cyclopropyl ethyl ether; and medium or higher alkyl ethers such as octyl ether, diethylhexyl ether, lauryl ether and cetyl ether; unsaturated ethers such as oleyl ether and linolenyl ether; lower alkenyl ethers such as vinyl ether, allyl ether; lower alkynyl ethers such as ethynyl ether and propynyl ether; hydroxy(lower)alkyl ethers such as hydroxyethyl ether and hydroxyisopropyl ether; lower alkoxy (lower)alkyl ethers such as methoxymethyl ether and 1-methoxyethyl ether; optionally substituted aryl ethers such as phenyl ether, tosyl ether, t-butylphenyl ether, salicyl ether, 3,4-di-methoxyphenyl ether and benzamidophenyl ether; and aryl(lower)alkyl ethers such as benzyl ether, trityl ether and benzhydryl ether.

Examples of the esters include aliphatic esters, for example, lower alkyl esters such as methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester and 1-cyclopropylethyl

ester; lower alkenyl esters such as vinyl ester and allyl ester; lower alkynyl esters such as ethynyl ester and propynyl ester; hydroxy(lower)alkyl ester such as hydroxyethyl ester; lower alkoxy (lower) alkyl esters such as methoxymethyl ester and 1-methoxyethyl ester; and optionally substituted aryl esters such as, for example, phenyl ester, tolyl ester, t-butylphenyl ester, salicyl ester, 3,4-di-methoxyphenyl ester and benzamidophenyl ester; and aryl(lower)alkyl ester such as benzyl ester, trityl ester and benzhydryl ester.

The amide of A mean a group represented by the formula -CONR'R", wherein each of R' and R" is hydrogen, lower alkyl, aryl, alkyl- or aryl-sulfonyl, lower alkenyl and lower alkynyl, and include for example lower alkyl amides such as methylamide, ethylamide, dimethylamide and diethylamide; arylamides such as anilide and toluidide; and alkyl- or aryl-sulfonylamides such as methylsulfonylamide, ethylsulfonyl-amide and tolylsulfonylamide.

Preferred examples of L and M include hydroxy and oxo, and especially, M is hydroxy and L is oxo which has a 5-membered ring structure of, so called, PGE type.

Preferred example of A is -COOH, its pharmaceutically acceptable salt, ester or amide thereof.

Preferred example of X_1 and X_2 is fluorine, so called, for example, 16,16-difluoro type.

Preferred R_1 is a hydrocarbon residue containing 1-10 carbon atoms, preferably 6-10 carbon atoms. Further, at least one carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur.

Examples of R_1 include, for example, the following groups:

$-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-$,

$-CH_2-CH=CH-CH_2-CH_2-CH_2-$,

$-CH_2-CH_2-CH_2-CH_2-CH=CH-$,

$-CH_2-C\equiv C-CH_2-CH_2-CH_2-$,

$-CH_2-CH_2-CH_2-CH_2-O-CH_2-$,

$-CH_2-CH=CH-CH_2-O-CH_2-$,

$-CH_2-C\equiv C-CH_2-O-CH_2-$,

$-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-$,

$-CH_2-CH=CH-CH_2-CH_2-CH_2-CH_2-$,

$-CH_2-CH_2-CH_2-CH_2-CH_2-CH=CH-$,

$-CH_2-C\equiv C-CH_2-CH_2-CH_2-CH_2-$,

$-CH_2-CH_2-CH_2-CH_2-CH_2-CH(CH_3)-CH_2-$,

$-CH_2-CH_2-CH_2-CH_2-CH(CH_3)-CH_2-$,

$-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-$,

$-CH_2-CH=CH-CH_2-CH_2-CH_2-CH_2-CH_2-$,

$-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH=CH-$,

$-CH_2-C\equiv C-CH_2-CH_2-CH_2-CH_2-CH_2-$, and

$-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH(CH_3)-CH_2-$.

Preferred Ra is a hydrocarbon containing 1-10 carbon atoms, more preferably, 1-8 carbon atoms. Ra may have one

or two side chains having one carbon atom.

The configuration of the ring and the α- and/or ω chains in the above formula (I) and (II) may be the same as or different from that of the primary PGs. However, the present invention also includes a mixture of a compound having a primary type configuration and a compound of a non-primary type configuration.

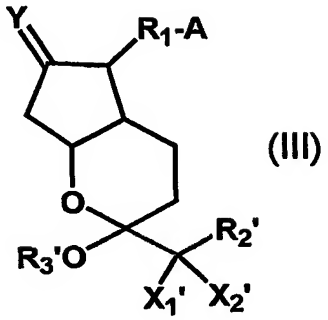
In the present invention, the PG compound which is dihydro between 13 and 14, and keto(=O) at 15 position may be in the keto-hemiacetal equilibrium by formation of a hemiacetal between hydroxy at position 11 and keto at position 15.

For example, it has been revealed that when both of X_1 and X_2 are halogen atoms, especially, fluorine atoms, the compound contains a tautomeric isomer, bicyclic compound.

If such tautomeric isomers as above are present, the proportion of both tautomeric isomers varies with the structure of the rest of the molecule or the kind of the substituent present. Sometimes one isomer may predominantly be present in comparison with the other. However, it is to be appreciated that the present invention includes both isomers.

Further, the 15-keto-PG compounds used in the invention include the bicyclic compound and analogs or derivatives thereof.

The bicyclic compound is represented by the formula (III)



(III)

wherein, A is $-CH_3$, or $-CH_2OH$, $-COCH_2OH$, -COOH or a functional derivative thereof;

X_1'and X_2'are hydrogen, lower alkyl, or halogen;

Y is

wherein R_4'and R_5' are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R_4'and R_5'are not hydroxy and lower alkoxy at the same time.

R_1 is a saturated or unsaturated divalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

R_2' is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkoxy, lower

alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or hetrocyclic-oxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclic-oxy group.

R_3' is hydrogen, lower alkyl, cyclo(lower)alkyl, aryl or heterocyclic group.

Furthermore, while the compounds used in the invention may be represented by a formula or name based on keto-type regardless of the presence or absence of the isomers, it is to be noted that such structure or name does not intend to exclude the hemiacetal type compound.

In the present invention, any of isomers such as the individual tautomeric isomers, the mixture thereof, or optical isomers, the mixture thereof, a racemic mixture, and other steric isomers may be used in the same purpose.

Some of the compounds used in the present invention may be prepared by the method disclosed in USP Nos.5,073,569, 5,166,174, 5,221,763, 5,212,324, 5,739,161 and 6,242,485 these cited references are herein incorporated by reference).

According to the present invention a mammalian subject may be treated by the instant invention by administering the compound used in the present invention. The subject may be any mammalian subject including a human. The

compound may be applied systemically or topically. Usually, the compound may be administered by oral administration, intravenous injection (including infusion), subcutaneous injection, intra rectal administration, intra vaginal administration, transdermal administration and the like. The dose may vary depending on the strain of the animal, age, body weight, symptom to be treated, desired therapeutic effect, administration route, term of treatment and the like. A satisfactory effect can be obtained by systemic administration 1-4 times per day or continuous administration at the amount of 0.001-1000 μg/kg per day, more preferably 0.01-100 μg/kg, most preferably 0.1-10 μg/kg.

The compound may preferably be formulated in a pharmaceutical composition suitable for administration in a conventional manner. The composition may be those suitable for oral administration, injection or perfusion as well as it may be an external agent, suppository or pessary.

The composition of the present invention may further contain physiologically acceptable additives. Said additives may include the ingredients used with the prostaglandin compound such as excipient, diluent, filler, resolvent, lubricant, adjuvant, binder, disintegrator, coating agent, cupsulating agent, ointment base, suppository base, aerozoling agent, emulsifier, dispersing

agent, suspending agent, thickener, tonicity agent, buffering agent, soothing agent, preservative, antioxidant, corrigent, flavor, colorant, a functional material such as cyclodextrin and biodegradable polymer, stabilizer. The additives are well known to the art and may be selected from those described in general reference books of pharmaceutics.

The amount of the above-defined compound in the composition of the invention may vary depending on the formulation of the composition, and may generally be 0.00001-10.0 wt%, more preferably 0.0001-1.0 wt%, most preferably 0.001-0.1%.

Examples of solid compositions for oral administration include tablets, troches, sublingual tablets, capsules, pills, powders, granules and the like. The solid composition may be prepared by mixing one or more active ingredients with at least one inactive diluent. The composition may further contain additives other than the inactive diluents, for example, a lubricant, a disintegrator and a stabilizer. Tablets and pills may be coated with an enteric or gastroenteric film, if necessary. They may be covered with two or more layers. They may also be adsorbed to a sustained release material, or microcapsulated. Additionally, the compositions may be capsulated by means of an easily degradable material such

gelatin. They may be further dissolved in an appropriate solvent such as fatty acid or its mono, di or triglyceride to be a soft capsule. Sublingual tablet may be used in need of fast-acting property.

Examples of liquid compositions for oral administration include emulsions, solutions, suspensions, syrups and elixirs and the like. Said composition may further contain a conventionally used inactive diluents e.g. purified water or ethyl alcohol. The composition may contain additives other than the inactive diluents such as adjuvant e.g. wetting agents and suspending agents, sweeteners, flavors, fragrance and preservatives.

The composition of the present invention may be in the form of spraying composition, which contains one or more active ingredients and may be prepared according to a known method.

Examples of the injectable compositions of the present invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions. Diluents for the aqueous solution or suspension may include, for example, distilled water for injection, physiological saline and Ringer's solution.

Non-aqueous diluents for solution and suspension may include, for example, propylene glycol, polyethylene glycol, vegetable oils such as olive oil, alcohols such as ethanol

and polysorbate. The composition may further comprise additives such as preservatives, wetting agents, emulsifying agents, dispersing agents and the like. They may be sterilized by filtration through, e.g. a bacteria-retaining filter, compounding with a sterilizer, or by means of gas or radioisotope irradiation sterilization. The injectable composition may also be provided as a sterilized powder composition to be dissolved in a sterilized solvent for injection before use.

The present external agent includes all the external preparations used in the fields of dermatology and otolaryngology, which includes ointment, cream, lotion and spray.

Another form of the present invention is suppository or pessary, which may be prepared by mixing active ingredients into a conventional base such as cacao butter that softens at body temperature, and nonionic surfactants having suitable softening temperatures may be used to improve absorbability.

The term "treatment" used herein includes any means of control such as prevention, care, relief of the condition, attenuation of the condition and arrest of progression.

The pharmaceutical composition of the present invention may further contain other pharmacological ingredients as far as they do not contradict the purpose of

the present invention.

The further details of the present invention will follow with reference to test examples, which, however, are not intended to limit the present invention.

Example

13,14-dihydro-15-keto-16,16-difluoro-PGE_1 was used as the test substance. Test capsule for oral administration containing 24 μg of the test substance and placebo capsule made from inert ingredients which was identical to the test capsule were prepared.

Volunteers were divided into 4 groups. The test groups received 24, 48 and 72 μg of the test substance per day respectively and the control group received the placebo. All volunteers were instructed to take one capsule before each meal (morning-, day- and evening-time) everyday for 21 days. Test group I (27 volunteers) received 24 μg of the test substance per day by taking the test capsule at the morning time and the placebo capsule at each of the day and evening times; test group II (32 volunteers) received 48 μg of the test substance per day by taking the test capsule at each of the morning and evening times and the placebo capsule at the day time; test group III (32 volunteers) received 72 μg of the test substance by taking the test capsule three times per day. Control group (33 volunteers) received the placebo capsule every time. Volunteers were

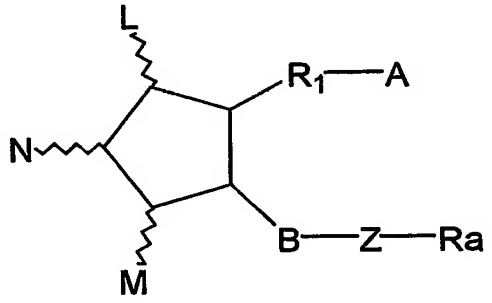
instructed to take each capsule with 8 ounces of water prior to eating a meal. Body weight was measured before and 3 weeks after the initiation of the administration.

Fig.1 shows the changes of body weight from the pre-values in each group at 3 weeks after the initiation of the administration. As shown in Fig.1, body weight reductions were observed in all test groups while an increase was observed in the control group. The body weight of the test groups decreased in a dose dependent manner.

CLAIMS

1. A method for treating obesity in a mammalian subject, which comprises administration of an effective amount of a prostaglandin compound to the subject.

2. The method as described in Claim 1, wherein said prostaglandin compound is the compound as shown by the following general formula (I).



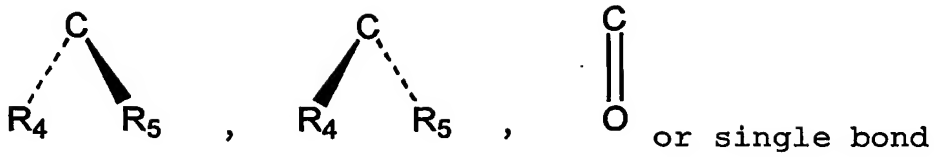
(I)

wherein L, M and N are hydrogen atom, hydroxy, halogen atom, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is $-CH_3$, or $-CH_2OH$, $-COCH_2OH$, $-COOH$ or a functional derivative thereof;

B is single bond, $-CH_2-CH_2-$, $-CH=CH-$, $-C\equiv C-$, $-CH_2-CH_2-CH_2-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-C\equiv C-CH_2-$ or $-CH_2-C\equiv C-$;

Z is

 or single bond

wherein R_4 and R_5 are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R_4 and R_5 are not hydroxy and lower alkoxy at the same time;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

Ra is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or hetrocyclic-oxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclic-oxy.

3. The method as described in Claim 1, wherein said prostaglandin compound is 16-mono or dihalogen-prostaglandin compound.

4. The method as described in Claim 1, wherein said

prostaglandin compound is 13,14-dihydro-16-mono or dihalogen-prostaglandin compound.

5. The method as described in Claim 1, wherein said prostaglandin compound is 13,14-dihydro-15-keto-16-mono or dihalogen-prostaglandin compound.

6. The method as described in Claim 1, wherein said prostaglandin compound is 13,14-dihydro-16-mono or difluoro-prostaglandin compound.

7. The method as described in Claim 1, wherein said prostaglandin compound is 13,14-dihydro-15-keto-16-mono or difluoro-prostaglandin compound.

8. The method as described in Claim 1, wherein said prostaglandin compound is 13,14-dihydro-16-mono or dihalogen-prostaglandin E compound.

9. The method as described in Claim 1, wherein said prostaglandin compound is 13,14-dihydro-15-keto-16-mono or dihalogen-prostaglandin E compound.

10. The method as described in Claim 1, wherein said prostaglandin compound is 13,14-dihydro-16,16-difluoro - prostaglandin E_1 compound.

11. The method as described in Claim 1, wherein said prostaglandin compound is 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E_1 compound or 13,14-dihydro-15-keto- 16,16-difluoro-18-methyl-prostaglandin E_1 compound.

12. The method as described in Claim 1, which comprises

systemic administration 1-4 times per day or continuous administration at the amount of 0.01-100μg/kg per day.

13. The method as described in Claim 12, wherein the administration is at the amount of 0.1-10μg/kg per day.

14. A composition for treating obesity, which comprises a prostaglandin compound as active ingredient thereof.

15. A use of a prostaglandin compound for manufacturing a medicament for treating obesity.

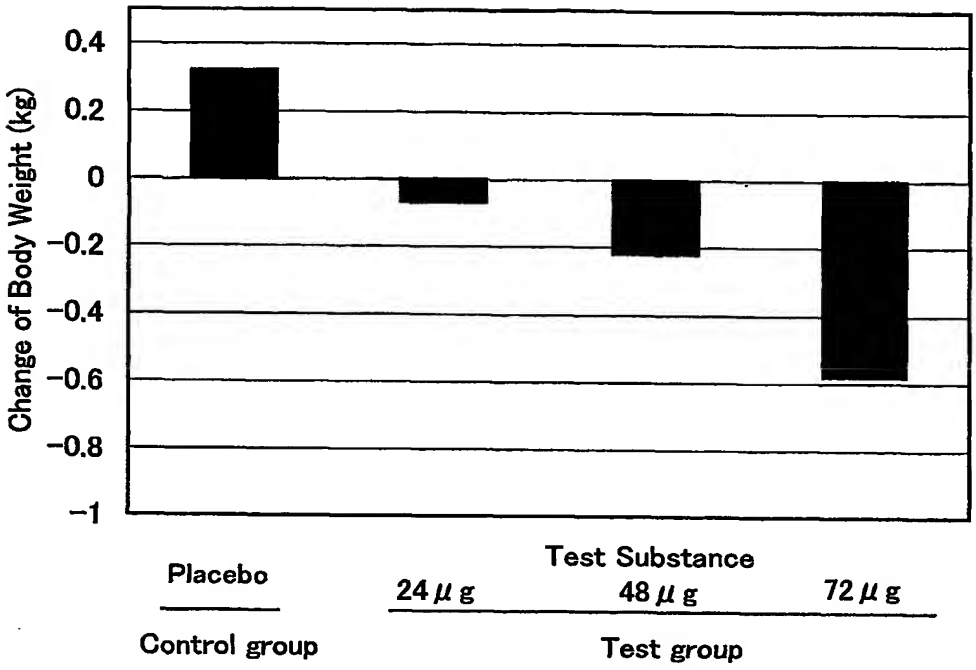

0.4
0.2
0
−0.2
−0.4
−0.6
−0.8
−1
Change of Body Weight (kg)
Placebo
24 μ g
48 μ g
72 μ g
Test Substance
Control group
Test group

Figure 1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/[redacted]03/13453

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/5575 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, WPI Data, PAJ, EMBASE, BIOSIS, CHEM ABS Data, PASCAL, SCISEARCH, CANCERLIT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 33724 A (EVANS ROLAND M ;FORMAN BARRY M (US); SALK INST FOR BIOLOGICAL STUD) 31 October 1996 (1996-10-31) page 3, line 5 - line 9 page 4, line 12 -page 7, line 24 page 19, line 15 -page 20, line 14	1,2, 12-15
Y	the whole document	3-11
X	US 3 888 919 A (SCHNEIDER WILLIAM P ET AL) 10 June 1975 (1975-06-10) column 7, line 59 -column 8, line 7	1,2, 12-15

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 February 2004	27/02/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Albrecht, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internat[redacted] Application No
PCT[redacted]03/13453

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 53927 A (TUFTS COLLEGE ;GREENBERG ANDREW S (US)) 28 October 1999 (1999-10-28) page 6, line 13 -page 7, line 2 page 9, line 21 - line 27 page 17, line 15 - line 16 page 18, line 1 - line 7 page 40, line 1 - line 19	1,2, 12-15
Y	the whole document	3-11
X	POLIS E ET AL: "Dose-dependent reduction of hereditary obesity in the non-diabetic mouse by polymeric prostaglandin PGBx." PHYSIOLOGICAL CHEMISTRY AND PHYSICS. UNITED STATES 1980, vol. 12, no. 6, 1980, pages 564-568, XP009026227 ISSN: 0031-9325 page 565 - page 567, chapters "Results" and "Discussion"	1,14,15
Y	EP 0 410 646 A (UENO SEIYAKU OYO KENKYUJO KK) 30 January 1991 (1991-01-30) page 2, line 44 -page 3, line 15 page 12, line 41 - line 50 Formulation examples	3-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 03/13453

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/[redacted]03/13453

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			DE	69006964 T2	09-06-1994
			EP	0410646 A2	30-01-1991
			JP	3163024 A	15-07-1991
			JP	8005794 B	24-01-1996
			US	5234954 A	10-08-1993